REMARKS

Claims 1-35 are pending in the present application. Claims 1-35 were variously rejected under 35 U.S.C. §112, first paragraph, claims 29-35 were rejected under 35 U.S.C. §112, second paragraph, claims 29-32 and 35 were rejected under 35 U.S.C. § §102(a) and 102(e), and claims 10-14, 16-19, 20-24, 26-28, 29-33 and 35 were rejected under 35 U.S.C. §102(b).

Applicant has not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Applicant has carefully considered the points raised in the Office Action and believes that the Examiner's concerns have been addressed as described herein, thereby placing this case into condition for allowance. Reconsideration of the rejections contained in the Office Action is respectfully requested.

Rejections under 35 U.S.C. §112, first paragraph

A. Claims 1-9 and 29-35 were rejected under 35 U.S.C. §112, first paragraph, as allegedly nonenabled. Applicant respectfully traverses this rejection.

With respect to the enablement requirement for patentability, the burden is on the Examiner to show that the specification is not enabling. MPEP § 2164.04 states that "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." The MPEP cites the decision in *In re Marzocchi*, 439 F.2d 220, 224 (CCPA 1971), in which the court held that the Patent Office, when making a rejection on the basis of nonenablement, must

explain why it doubts the truth or accuracy of the disclosure by backing up its assertion with acceptable contrary evidence or reasoning. Applicant respectfully submits that the Examiner has failed to meet this burden. There is no evidence or reasoning provided in the Office Action that would serve to rebut the presumption that the disclosure provided in the specification is enabling. Each basis for alleged nonenablement by the Examiner, namely, (a) alleged lack of sufficient guidance, and (b) unpredictability of gene therapy, has been addressed, as discussed below.

As an initial matter, Applicant traverses the Examiner's assertion that "[t]he specification does not disclose the use of said ISS in preventing the symptoms of a human or animal herpes simplex virus infection" (Office Action, page 4). Such uses are disclosed, for example, on pages 19-21 of the specification, which describe, *inter alia*, "methods for preventing one or more symptoms of herpes virus infection" (page 19, lines 18-19) by administering "[a]n ISS-containing composition which does not include a herpes virus antigen . . . to an individual at risk of exposure to, exposed to, infected with and/or exhibiting one or more symptoms of infection by *alphaherpesvirinae*" (page 19, lines 24-27). Administration of an ISS-containing polynucleotide after exposure to a herpes virus but prior to appearance of symptoms of herpes virus infection is also disclosed, for example, on page 34, lines 11-14, and on page 35, lines 4-5.

The Examiner also states that "the specification does not teach how the administration of the ISS sequences leads to the prevention of symptom development since it has not been shown in mice and guinea pigs that were used as the models in the instant application." Office Action, page 4. Applicant respectfully points out that prevention of symptom development after herpes virus exposure was observed in the mouse model used in Example 1. At page 44, lines 3-4, the specification reports that "treatment with ISS resulted in decreased incidence (*i.e.*, individuals showing symptoms of HSV-2 infection)." Thus, contrary to the Examiner's statement, the specification exemplifies preventing symptom development after exposure to a herpes simplex virus.

In addition to the exemplified support for prevention of a herpes virus symptom, the specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention for prevention of a symptom of herpes simplex virus infection. Applicant respectfully traverses the Examiner's assertion that insufficient guidance is provided. Examples of ISS-containing polynucleotides and methods for their synthesis are provided, for example, on pages 20-29. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on pages 35-36. Examples of dosage ranges are provided, for example, on page 36. Examples of means of administration are provided, for example, on pages 37-38. Means for assessment of prevention of one or more symptoms of herpes simplex virus infection are provided, for example, on pages 38-40. Examples of kits of the invention are provided on pages 40-42. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation.

The Examiner also states that "the unpredictability of gene therapy . . . would have required a skilled artisan to engage in undue experimentation to practice the invention to prevent a symptom of herpes simplex virus infection" (Office Action, pages 6-7). As discussed more fully below, the present invention does not encompass "gene therapy." Therefore, the Examiner's statement does not apply to and is not appropriate to an analysis of the claims at issue.

The Examiner discusses the unpredictability of gene therapy, citing Verma et al. (*Nature* 389:239-242 (1997)), Marshall (*Science* 269:1050-1055 (1995)), and Orkin (*Report and Recommendations of the Panel to Assess the NIH Investment in Research on Gene Therapy* (Dec. 7, 1995)). Applicant respectfully submits that this basis is irrelevant with regard to the present invention, which uses immunostimulatory polynucleotide sequences. As defined in Verma et al., gene therapy encompasses "putting *corrective genetic material* into cells [to alleviate] the symptoms of disease" (Verma, page 239, emphasis added). Further, Orkin defines gene therapy

as a "a set of approaches to the treatment of human disease based on the transfer of *genetic material* (DNA) into an individual" (Orkin, page 3, emphasis added), discussing approaches such as "gene addition" to correct a single-gene inherited disorder, transfer of genes for cytokines as a treatment for cancer, and transfer of modified genes for viruses such as HIV as an approach to developing new vaccines (Orkin, pages 5-7). Gene therapy generally involves delivery of a transgene containing coding sequences for a gene of interest into a cell (see, *e.g.*, Verma, Fig. 1). In contrast, the present invention involves administering an immunostimulatory sequence to prevent or ameliorate a symptom of herpes simplex virus infection, rather than introduction of a gene to correct a genetic defect or to increase production of a naturally-occurring or modified protein. The Examiner's arguments with respect to the unpredictability of gene therapy are therefore moot with regard to the present invention.

The Examiner discusses Mountain (*TIBTECH* 18:119-128 (2000)) and Romano et al. (*Stem Cells* 18:19-39 (2000)) as allegedly disclosing that "naked DNA delivery results in lower delivery efficiency than vectors, brief expression in most tissues and unsuitability for targeting" (Office Action, page 5, citing Mountain) and that these limitations "make difficult the in vivo applications of nonviral gene delivery systems" (Office Action, page 5, quoting Romano et al.). The cited references discuss developments in the field of gene therapy, which as discussed above, does not relate to the present invention. For example, Mountain defines gene therapy as "the treatment or prevention of disease by gene transfer" (Mountain, page 119). The present invention does not involve transfer of a gene. The quoted passage from Romano et al. is part of a discussion of low transfection efficiency and transient transgene expression when using nonviral gene delivery systems for gene therapy applications (Romano, page 30). The present invention does not involve transgene expression. Therefore, the Examiner's arguments with respect to these references do not apply to the present invention.

The Examiner discusses Krieg (*Journal of Gene Medicine* 1:56-63 (1999)) and Tokunaga (*Jpn. J. Infect. Dis.* 52:1-11 (1999)) in the context of gene therapy. The Examiner states that

Krieg states that immunostimulatory CpG motifs "may have an unwanted effect of acute inflammatory response . . . and further suggests that the generation of immune responses is to be avoided in any *gene therapy* application" (Office Action, page 6, emphasis added). As discussed above, the present invention does not involve gene therapy, defined in Krieg as expression of an encoded gene from a vector (Krieg, page 60).

The Examiner states that Tokunaga states that "activation of the immune system with ISS DNA could cause both beneficial as well as deleterious consequences," citing development of systemic lupus erythematosis possibly attributed to the ISS in bacterial DNA (Office Action, page 6). The present claims are directed to methods and kits for preventing or ameliorating a symptom of herpes simplex virus infection. Applicant respectfully submits that the possibility of a side effect is not proper basis for a lack of enablement rejection.

In summary, (a) there is sufficient guidance provided in the specification and (b) this invention is not directed to gene therapy. Thus, both grounds for alleged nonenablement do not support the Examiner's position.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 1-9 and 29-35 under 35 U.S.C. § 112, first paragraph.

B. Claims 10-19 and 20-28 were rejected under 35 U.S.C. §112, first paragraph, as allegedly nonenabled. Applicant respectfully traverses this rejection.

As an initial matter, Applicant traverses the Examiner's assertion that the "nature of the invention of claims 10-28 is directed to gene therapy with ISS" (Office Action, page 7) for the reasons discussed above. The present invention does not relate to gene therapy.

The Examiner admits that the specification is enabling for a method of reducing severity and/or recurrence of a symptom of herpes simplex virus 2 infection in mice and guinea pigs, but states that the specification "does not reasonably provide enablement for a method of reducing the severity of a symptom of HSV-2 infection in any individual or mammal" (Office Action,

page 7). The Examiner appears to be referring to the Examples, which disclose administration of an ISS to mice and guinea pigs. As the Examiner states, analysis of enablement requires consideration of eight factors (MPEP § 2164.01(a)).[1] Office Action, pages 2-3. Applicant respectfully points out that using only one of the factors (*i.e.*, existence of working examples) is improper. All eight *Wands* factors must be considered in an enablement analysis.

In addition to the exemplified support for prevention of a herpes virus symptom, the specification in its entirety provides sufficient guidance to teach one of skill in the art how to make and use the invention for reducing severity and reducing recurrence of a symptom of herpes simplex virus infection. Applicant respectfully traverses the Examiner's assertion that insufficient guidance is provided.

The specification provides adequate guidance to enable one of skill in the art to make and use the claimed invention. Examples of ISS-containing polynucleotides and methods for their synthesis are provided, for example, on pages 20-29. Examples of administration regimens are provided, for example, on pages 34-35. Examples of formulations are provided, for example, on pages 35-36. Examples of dosage ranges are provided, for example, on page 36. Examples of means of administration are provided, for example, on pages 37-38. Means for assessment of reducing severity and reducing recurrence of one or more symptoms of herpes simplex virus infection are provided, for example, on pages 38-40. Such extensive disclosure provides adequate guidance such that a skilled artisan would be able to practice the invention without undue experimentation. The burden is on the Examiner to show that the specification is not enabling (MPEP § 2164.04).

With respect to the Examiner's assertion that enablement for mice and guinea pigs is insufficient to provide enablement for "any individual or mammal," Applicant respectfully points out that it is a well-established principle of patent law that "patent applicants are not required to

---

[1] *Wands* factors for enablement analysis, as set forth in *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988).

disclose every species encompassed by their claims, even in an unpredictable art." *In re Vaeck*, 947 F.2d 488, 496 (Fed. Cir. 1991). In *In re Angstadt*, the Court of Customs and Patent Appeals considered the issue of whether section 112 requires disclosure of a test with every species covered by a claim and concluded that requirement of such a complete disclosure would necessitate a patent application with thousands of examples and "would force an inventor seeking adequate patent protection to carry out a prohibitive number of actual experiments." *In re Angstadt*, 537 F.2d 498, 502 (CCPA 1976). The court concluded that such a requirement would be against public policy because it would have the effect of "depriving inventors of claims which adequately protect them and [would limit] them to claims which practically invite appropriation of the invention while avoiding infringement[, which would] inevitably [have] the effect of suppressing disclosure." *Id.* at 504. In conclusion, based on the foregoing, Applicant traverses the suggestion that enablement in mice and guinea pigs is insufficient to enable the invention as claimed, particularly in view of the disclosure in the specification.

MPEP §2164.02 states that an "*in vivo* animal model example in the specification, in effect, constitutes a "working example" if that example "correlates" with a disclosed or claimed method invention" and that ""[c]orrelation" as used herein refers to the relationship between *in vitro* or *in vivo* animal model assays and a disclosed or a claimed method of use." The same section of MPEP also states that "if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate."

It is described in the specification, for example, on page 13, lines 1-9, and is well known in the art that the murine and guinea pig models used in this application are art-accepted models for the study of herpes simplex virus infection.[2] For example, on page 78, Parr et al. ((1997) *J. Reprod. Immunol.* 36:77-92, of record) state that "[t]wo animal models have mainly been used in

---

[2] See, for example, Bourne et al. ((1996) *J. Infect. Dis.* 173:800-807, of record), page 800, column 2; Stanberry ((1995) *Trends Microbiol.* 3:244-247, of record), page 245, column 1.

evaluation of experimental HSV vaccines: a lethal challenge model in mice ... and a guinea pig model that exhibits cutaneous herpetic disease." Therefore, Applicant traverses the contention that enablement in these animal models is insufficient to enable the invention as claimed.

The Examiner discusses Kmiec (*American Scientist* 87:240-247 (1999)) for the proposition that "animal models are not truly reflective of success in humans and are thus not predictive" (Office Action, page 8). Kmiec discusses the status of gene therapy techniques, defined in this reference as delivery to the nucleus of a cell of a correct version of a mutated gene, the expression of which will produce the normal protein and hence restore normal cellular function (Kmiec, page 241). As discussed above, the present invention does not relate to gene therapy. The claims do not involve delivery of a correct version of a mutated gene to the nucleus of a cell to restore normal cellular function. The discussion in Kmiec with regard to animal models is not in the context of herpes virus infection or in the use of the claimed ISS. Therefore, this reference is inapplicable to the claimed invention.

Further, it is not necessary for Applicant to provide experimental data for every species claimed in order for the invention to be enabled, as discussed above.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under § 112, first paragraph.

Rejections under 35 U.S.C. §112, second paragraph

Claims 29-35 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Applicant respectfully traverses this rejection.

Claim 29 recites that the kit comprises instructions for administration of the claimed composition.

The Examiner asserts that the claims "are indefinite in their recitation of "instructions for administration ...". It is unclear what the instructions would say." Office Action, page 9.

Applicant traverses this assertion and submits that the phrase "instructions for administration" is clear within the context of claim 29 in its entirety. In addition, the specification describes that instructions in the kits of the invention "generally include information as to dosage, dosing schedule, and route of administration for the intended treatment." Page 41, lines 12-14. Thus, Applicant submits that claims are sufficiently definite when considered in view of the specification and the understanding of those of skill in the art.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 29-35 under 35 U.S.C. § 112, second paragraph.

Rejection under 35 U.S.C. §102(a)

Claims 29-32 and 35 were rejected under 35 U.S.C. §102(a) as allegedly being anticipated by Krieg (1999, *Journal of Gene Medicine*, vol. 1, pp. 56-63). Applicant respectfully traverses this rejection.

In order to anticipate, a reference must disclose each and every element of a claimed invention. The Examiner alleges that Krieg teaches all the limitation of claims 29-32 and 35. Office Action, page 10. Applicant respectfully traverses.

Krieg describes polynucleotides containing immune stimulatory CpG-S motifs and immune neutralizing CpG-N motifs and the use of such motifs in genetic vaccination and gene therapy. However, Krieg does not teach the claimed invention, i.e., a kit for use in ameliorating or preventing a symptom of herpes simplex virus infection, comprising a composition comprising an ISS and instructions for use, wherein the kit does not comprise a herpes simplex virus antigen.

Krieg does not disclose a kit comprising a composition comprising an ISS-containing polynucleotide nor a kit that does not comprise a herpes simplex virus antigen. Krieg does not disclose the claimed element of instructions for administration of the composition to an individual infected with, exposed to or at risk of being exposed to herpes simplex virus. In

addition, Krieg does not mention herpes virus. Accordingly, as it does not disclose each and every element of claims 29-32 and 35, Krieg does not anticipate the claimed invention.

The Examiner's assertion that "mere printed matter cannot impart a patentable feature to a claim" (Office Action, page 10) is incorrect. The case cited by the Examiner in support of this assertion, *In re Gulack*, 217 USPQ 401 (1983), actually reaches the opposite result.[3] In *In re Gulack*, the Federal Circuit held that "[d]ifferences between an invention and the prior art cited against it cannot be ignored merely because those differences reside in the content of the printed matter." *In re Gulack*, 703 F.2d 1381, 1384 (Fed. Cir. 1983). The *Gulack* court also referred to a previous decision by the U.S. Court of Customs and Patent Appeals which held that "[p]rinted matter may very well constitute structural limitations upon which patentability can be predicated." *In re Royka*, 490 F.2d 981, 985 (CCPA 1974). In overturning a §103 rejection by the Board of Appeals, based on the proposition that the recitation of printed matter in claims is not accorded patentable weight, the *Gulack* court stated, "the board cannot dissect a claim, excise the printed matter from it, and declare the remaining portion of the mutilated claim to be unpatentable. *The claim must be read as a whole.* If the board meant to disregard that basic principle of claim interpretation, we must reverse the rejection as a matter of law." *Gulack* at 1385 (emphasis added). The Examiner has done precisely what the *Gulack* court admonished against, by excising the printed matter from the claim and declaring the remaining portion of the claim to be unpatentable, and therefore has used an improper legal basis for rejection. The correct legal standard is a determination of whether there is a functional relationship between the printed matter and the substrate. *Gulack* at 1385. In the present claims, there is a functional relationship between instructions for administration of the composition and the composition comprising an ISS which must be administered.

---

[3] The issues in *In re Gulack* were based on a 35 U.S.C. § 103 rejection. The Examiner is improperly using an obviousness case to support a 35 U.S.C. § 102(a) rejection.

Finally, the Examiner also points to the MPEP and cites *In re Casey*, 152 USPQ 235 (CCPA 1967), in support of this rejection of the kit claims. The section of the MPEP that references *In re Casey*, states that "this line of cases is limited to claims directed to machinery which works upon an article or material in its intended use. It does not apply to product claims or kit claims." MPEP § 2115.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 29-32 and 35 under 35 U.S.C. § 102(a).

Rejection under 35 U.S.C. §102(b)

Claims 10-14, 16-19, 20-24, 26-28, 29-33 and 35 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Schwartz et al. (WO 98/55495, "Schwartz"). Applicant respectfully traverses this rejection.

The claimed invention is directed to a method of reducing severity of a symptom of herpes simplex virus infection and to a method of reducing recurrence of a symptom of herpes simplex virus infection. The methods include administration of an ISS-containing polynucleotide composition in the absence of administration of a herpes simplex virus antigen. The invention is also directed to a kit for use in ameliorating or preventing a symptom of herpes simplex virus infection, comprising a composition comprising an ISS and instructions for use, wherein the kit does not comprise a herpes simplex virus antigen.

Schwartz describes the use of ISS-containing polynucleotides only in conjunction with an antigen for preventing a herpes virus infection (see page 5, lines 32-37). Contrary to the Examiner's statement that the reference teaches "an ISS sequence for treating herpes" (Office Action, page 11), Schwartz does not disclose the use of an ISS-containing polynucleotide for treating an individual infected with herpes simplex virus, much less for reducing severity or recurrence of a symptom of herpes virus infection. Schwartz does not disclose a kit for use in ameliorating or preventing a symptom of herpes simplex virus infection where the kit includes a

composition comprising an ISS and instructions for use, but where the kit does not include a herpes simplex virus antigen. As it does not disclose each and every element of claims 10-14, 16-19, 20-24, 26-28, 29-33 and 35, Schwartz does not anticipate the claimed invention.

Accordingly, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. §102(b).

Rejection under 35 U.S.C. §102(e)

Claims 29-32 and 35 were rejected under 35 U.S.C. §102(e) as allegedly being anticipated by Krieg et al. (US Patent No. 6,218,371, "the '371 patent"). Applicant respectfully traverses this rejection.

The Examiner alleges that the '371 patent teaches all the limitation of claims 29-32 and 35. (Office Action, page 12). Applicant respectfully traverses.

The '371 patent describes co-administration of an ISS and a cytokine, which are disclosed as acting synergistically to produce an anti-tumor response. However, the '371 patent does not teach the claimed invention, i.e., a kit for use in ameliorating or preventing a symptom of herpes simplex virus infection, comprising a composition comprising an ISS and instructions for use, wherein the kit does not comprise a herpes simplex virus antigen.

The '371 patent does not disclose a kit comprising a composition comprising an ISS-containing polynucleotide nor a kit that does not comprise a herpes simplex virus antigen. The '371 patent does not disclose the claimed element of instructions for administration of the composition. Accordingly, as it does not disclose each and every element of claims 29-32 and 35, the '371 patent does not anticipate the claimed invention.

As addressed above in response to the rejection under 35 U.S. C. § 102(a), the Examiner's assertion that "mere printed matter cannot impart a patentable feature to a claim" (Office Action, page 12) is incorrect. In the present claims, there is a functional relationship

between instructions for administration of the composition and the composition comprising an ISS which must be administered.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection of claims 29-32 and 35 under 35 U.S.C. § 102(e).

CONCLUSION

Applicant believes that all issues raised in the Office Action have been properly addressed in this response. Accordingly, reconsideration and allowance of the pending claims is respectfully requested. If it is determined that a telephone conversation would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket no. 377882001100. However, the Assistant Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Respectfully submitted,

Dated: October 9, 2002 By: Karen R Zachow

Karen R. Zachow
Registration No. 46,332

Morrison & Foerster LLP
3811 Valley Centre Drive
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5191
Facsimile: (858) 720-5125